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Plumpton, Catrin; Alfirevic, Ana; Pirmohamed, Munir; Hughes, Dyfrig

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Title

Cost effectiveness analysis of *HLA-B*58:01* genotyping prior to initiation of allopurinol for gout

Authors

Catrin O. Plumpton PhD¹, Ana Alfirevic MD PhD², Munir Pirmohamed MB ChB PhD², and Dyfrig A. Hughes PhD^{1,2}

¹Centre for Health Economics and Medicines Evaluation, Bangor University, Wales, UK

²Department of Molecular and Clinical Pharmacology, University of Liverpool, Liverpool, UK

*Author for correspondence: Professor Dyfrig Hughes, Centre for Health Economics and Medicines Evaluation, Bangor University, Ardudwy, Normal Site, Holyhead Road, Bangor, Wales, UK, LL57 2PZ. E-mail: d.a.hughes@bangor.ac.uk Telephone: +44(0)1248 382950

Short title

Allopurinol and *HLA-B*58:01* genotyping

Abstract

Objective: To determine whether prospective testing for *HLA-B*58:01*, as a strategy to prevent serious adverse reactions to allopurinol in patients with gout, is cost-effective from the perspective of the National Health Service in the UK.

Methods: A systematic review and meta-analysis for the association of *HLA-B*58:01* with cutaneous and hypersensitivity adverse drug reactions (ADRs) informed a decision analytic and Markov model to estimate lifetime costs and outcomes associated with testing versus standard care (with febuxostat prescribed for patients who test positive). Scenario analyses assessed alternative treatment assumptions and patient populations.

Results: The number of patients needed to test to prevent one case of ADR was 11,286 (95% Central Range, CR 2,573, 53,594). Cost and quality-adjusted life-year (QALY) gains were small £103 (95% CR £98, £106) and 0.0023 (95% CR -0.0006, 0.0055), resulting in an incremental cost-effectiveness ratio (ICER) of £44,954 per QALY gained. The probability of testing being cost-effective at a threshold of £30,000 per QALY was 0.25. Reduced costs of testing or febuxostat resulted in an ICER below £30,000 per QALY gained. The ICER for patients with chronic renal insufficiency was £38,478 per QALY gained.

Conclusion: Routine testing for *HLA-B*58:01* in order to reduce the incidence of adverse drug reactions in patients being prescribed allopurinol for gout is unlikely to be cost-effective in the UK; however testing is expected to become cost-effective with reductions in the cost of genotyping, and with the future availability of cheaper, generic febuxostat.

KEY WORDS: Allopurinol, Pharmacogenetics, Cutaneous adverse drug reaction, Cost-effectiveness analysis, *HLA-B*58:01*.

Introduction

Gout is a common inflammatory condition characterised by acute attacks (flares) which are episodes of severe joint pain, usually with redness, swelling, and tenderness of the joint; and is associated with increased risk of cardiovascular disease [1, 2]. Gout affects approximately 2.5% of the population and is most prevalent in older men [3].

Standard treatment for the long term management of gout includes urate lowering agents, with allopurinol accounting for 89% of prescriptions in the UK between 2000 and 2005 [4].

Allopurinol is generally well tolerated, but is associated with rare but severe cutaneous adverse drug reactions (SCARs) including Steven-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), affecting approximately 7 in 10,000 patients [5]. SCARs are associated with high mortality – up to 30% in the case of TEN [6]. Allopurinol is also associated with hypersensitivity adverse drug reactions (ADRs) (hereafter referred to as drug reaction with eosinophilia and systematic symptoms (DRESS)), including drug induced hypersensitivity syndrome (DIHS), also sometimes called allopurinol hypersensitivity syndrome (AHS) or hypersensitivity syndrome (HSS) [7].

Genetic association studies have identified the presence of the *HLA-B*58:01* allele to be an important risk factor for allopurinol-induced SJS or TEN, with an odds ratio of 96.6 (95%CI 24.5, 381.0) [8]. *HLA-B*58:01* is present in 15% to 18% of certain Asian populations but is less common (1% to 2%) in European populations [9]. Other risk factors for allopurinol hypersensitivity include high dose, renal impairment and concomitant use of diuretics [10].

While routine testing is not currently recommended by the Food and Drug Administration or the European Medicines Agency [11], the American College of Rheumatology guidelines note that genotyping should be considered in selected patients at elevated risk of ADRs,

including those with chronic renal insufficiency [12]. There are no randomised controlled trials of routine testing; however prospective cohort studies have suggested effectiveness in Taiwanese populations [13], and Korean patients with chronic renal insufficiency [14]. In both studies, patients who tested positive for *HLA-B*58:01* either avoided allopurinol or were administered allopurinol on a 28-day induction programme. No cases of SCAR occurred in either study, compared with expected rates of 0.3% [13] and 18% [14].

Many healthcare systems require evidence of efficiency for broader adoption of health technologies, including pharmacogenetics tests. Existing economic analyses have indicated that genotyping for *HLA-B*58:01* may be cost-effective in both Thailand and Korea [15, 16], but not in Singapore [17].

The aim of the present analysis is to estimate the cost-effectiveness of *HLA-B*58:01* genotyping prior to prescription of allopurinol in the UK healthcare setting.

Methods

Overview

A cohort model was used to track patients with chronic gout over a lifetime. Patients either receive allopurinol, or are first genotyped for *HLA-B*58:01* before being prescribed either allopurinol or febuxostat, conditional on test result. Febuxostat is recommended by the National Institute for Health and Care Excellence (NICE) in the UK as a second line treatment if allopurinol is not tolerated or is contraindicated. The analysis adopts the costing perspective of the National Health Service (NHS) in the UK assuming cost year 2014. Health outcomes were measured as quality-adjusted life-years (QALYs). Costs and QALYs were discounted after 1 year at a rate of 3.5% per annum. The base-case population was chosen

to be representative of the gout population in the UK, 81% male, with a mean age at diagnosis of 61.6 years [4].

The model, which is depicted in Figure 1, was adapted from the decision analysis of Beard et al [18] (2014), incorporating 3-month decision trees to capture the time during which the majority of serious ADRs are likely to occur [5, 19]. A Markov model, with a cycle length of 3 months and with half-cycle correction, captured the lifetime sequelae of SJS, TEN and DRESS, and the long term differences in costs and effectiveness of alternative urate lowering agents. States within the model were defined according to: (i) serum uric acid (sUA) concentration $< 360\mu\text{mol/l}$, (ii) $360\mu\text{mol/l} < \text{sUA} < 475\mu\text{mol/l}$, (iii) $475\mu\text{mol/l} < \text{sUA} < 595\mu\text{mol/l}$ and (iv) $\text{sUA} > 595\mu\text{mol/l}$, and reflect whether patients had experienced SJS, TEN or DRESS, with an option for (v) acute flares, and (vi) death (Figure 1). We assumed sUA to remain constant for individual patients, based on data from the EXCEL study, which indicated that 75% to 100% of patients who achieved $\text{sUA} < 360\mu\text{mol/l}$ maintained this over the remainder of the study [20].

insert figure 1 here

Treatment pathway

For standard care, all patients are prescribed allopurinol, titrated to 300mg/day during the first 3 months. Patients who are genotyped for *HLA-B*58:01* or who experience a serious ADR with allopurinol switch to febuxostat 80mg/day, given there is no evidence of cross-reactivity [21, 22]. Patients experiencing a serious ADR with febuxostat (which are far less likely) [23], discontinue urate lowering therapy altogether.

The clinical effectiveness for allopurinol, febuxostat and symptomatic flare management was considered in terms of the endpoint of reducing sUA to $< 360\mu\text{mol/l}$; consistent with existing clinical guidelines for the management of gout [12, 24, 25], and in terms of prevention (or in the prophylaxis period, provocation) of gout flares. Prophylactic treatment with colchicine ($500\mu\text{g}$ twice daily) was modelled for 3 months following initiation of allopurinol, or for 6 months following initiation of febuxostat [26]. The use of NSAIDs is assumed for all patients; but not probenecid, which is not listed in the British National Formulary.

Model parameters

Parameter estimates were obtained from purposive reviews of the literature and are listed in Table 1.

table 1 here

Clinical effectiveness

The risk-ratios for sUA $< 360\mu\text{mol/l}$ with febuxostat 80mg/day and allopurinol 300mg/day were taken from the Cochrane review and meta-analysis based on data from the FACT [30], APEX [30], and CONFIRMS [31] trials. The risk-ratio for achieving sUA to $< 360\mu\text{mol/l}$ with no treatment was taken from the Cochrane review and meta-analysis of studies comparing allopurinol 300mg/day and placebo [27].

For patients who did not achieve sUA $< 360\mu\text{mol/l}$, the distribution of patients across the 'non-response' sUA categories was allocated according to those indicated in Beard et al [18], taken from the FACT and APEX studies [29, 30]. The distribution of patients across sUA categories for no treatment was assumed to be the same as for allopurinol.

The probability of experiencing a flare during prophylaxis was taken from a pooled analysis of 8-week data from the FACT [29], APEX [30], and CONFIRMS trials [31] for allopurinol; and from a Cochrane review for febuxostat [28]. For subsequent model cycles, and for patients who were not prescribed urate lowering treatment, the probability of flares was determined by sUA concentration, as in Beard et al [18].

Prevalence of allopurinol induced SJS, TEN or DRESS

With a background population incidence of SJS/TEN of between 0.4 and 6 persons per million per year [15], and a risk ratio for allopurinol-induced SJS/TEN within the first 2 of initiation of 52 [19], the incidence of allopurinol induced SJS/TEN was calculated as being between 0.2 and 3 cases per 10,000 patients. Within the model we use a mean point estimate of 1.6 cases per 10,000 patients.

Data for DRESS were taken from a study of 1835 patients who were prescribed allopurinol, while monitored in a drug surveillance program [37].

Association between *HLA-B*58:01* and allopurinol induced SJS, TEN or DRESS

The systematic review by Somkura et al [8] was updated using PubMed (from inception up until August 2016) using the search terms (“HLA-B” OR “Human leukocyte antigen”) AND “allopurinol” AND (“Stevens Johnson Syndrome” OR “Toxic Epidermal Necrolysis” OR “Drug Reaction with Eosinophilia and Systematic Symptoms” OR “Drug Induced Hypersensitivity Syndrome” OR “Hypersensitivity Syndrome” OR “Allopurinol Hypersensitivity Syndrome”) or their acronyms. Search results were cross-referenced against the allelefrequencies database of studies of the association between *HLA-B*58:01* and allopurinol-induced ADR [9]. Studies were eligible for meta-analysis if they included an allopurinol tolerant control.

Meta-analysis was conducted using the *metandi* hierarchical logistic regression package in STATA (version 13; StataCorp LP, College Station, TX) [38] to determine the pooled sensitivity and specificity of the presence of *HLA-B*58:01* in predicting allopurinol induced SJS, TEN and DRESS.

Thirteen articles qualified for the meta-analysis (Appendix 1, 2). The pooled sensitivity of the 13 SJS/TEN studies was 0.95 (95% CI 0.90, 0.97), with specificity 0.88 (95% CI 0.84, 0.91).

Meta-analysis of data from 10 DRESS studies resulted in a pooled sensitivity of 0.93 (95% CI 0.84, 0.98) and specificity 0.85 (95% CI 0.65, 0.94).

Based on the prevalence of allopurinol induced SJS/TEN and DRESS, the positive predictive value (PPV) of genotyping for SJS/TEN is 0.0013, whilst the negative predictive value (NPV) of genotyping for SJS/TEN is 1.000. The corresponding values for DRESS are 0.0067 and 0.9999, respectively.

Allele prevalence

Pooled data for European populations (not restricted by ethnicity) resulted in an allele prevalence of 1.13% (95% CI 1.08%, 1.19%) [9].

Health state utilities

There is limited evidence linking health state utility with sUA concentrations or incidence of flares [39]. To date, all EQ-5D data reported in published economic evaluations have been sourced from an unpublished study of 417 patients from the UK, Germany and France [4, 18]. In the absence of alternative data, we assumed the same relationship of health utility and sUA, with an additional decrement in utility of 0.0097 applied for episodes of acute flares [18].

Utility decrements corresponding to SJS/TEN and DRESS were assigned as for severe burns [33] and sepsis [35], respectively, consistent with other economic evaluations [17, 36, 40]. Longer term disutilities to capture long term sequelae for SJS, TEN and DRESS (applied to the model from 3-months post ADR onwards) were taken from patient-level data for survivors of TEN [34].

Mortality

All-cause mortality was taken from UK life tables [32], adjusted by age and gender, whilst 3-month mortality for SJS/TEN and for DRESS were modelled at 26.5% (95% CI 18%, 24%) [6] and 10% (95% CI 5%, 15%) [7], respectively.

Costs

The total cost of gout maintenance treatment (£97.40 for 3 months) included consultation with General Practitioner, diagnostic tests (including sUA, serum creatinine and renal function), procedures (X-rays and joint aspiration) and hospitalisation due to complications of gout such as urinary tract infections or renal stones [18]. The total cost of flare management (£321.62 for the immediate treatment and management of an acute flare) included the costs of inpatient hospitalisation and outpatient clinic visits. The cost of allopurinol, febuxostat and colchicine were based on daily doses of 300mg (titrated over the course of the first cycle), 80mg and 1mg, respectively [26].

The costs of the acute management of SJS/TEN and DRESS reactions were based on a previous economic evaluation [36], in which data on healthcare resource use (e.g. treatments, procedures, length of hospitalisation according to intensity of care) were identified from a systematic review of the literature, and costed using NHS unit costs. We

found no evidence for the cost of long term management of SJS/TEN and so assumed that patients would require follow-up consultant appointments, which were costed based on 1 hour per annum. We further assumed there would be no cost incurred for managing sequelae of DRESS.

The cost of genotyping was based on a 2-stage process; an initial screen for *HLA-B*58* (£54.29) and, in patients who test positive, a second high resolution test for the specific *HLA-A*58:01* allele (£94.91) [36].

Analysis

Costs and QALYs were summed for genotyping prior to initiation of the urate lowering therapy, and for standard care (prescription of allopurinol without genotyping). The incremental cost-effectiveness ratio (ICER) was calculated as:

$$\text{ICER} = \frac{\text{Cost}_{\text{with test}} - \text{Cost}_{\text{standard care: no test}}}{\text{Outcome}_{\text{with test}} - \text{Outcome}_{\text{standard care: no test}}}$$

The economic evaluation was analysed in Microsoft Excel 2013, and reported according to the Consolidated Health Economic Evaluation Reporting Standards [41].

Sensitivity analysis

Parameter uncertainty was assessed by varying each parameter within its 95% confidence interval or, if unavailable, within a plausible range which, in the case of costs, was based on a standard deviation of 25% of the mean (Table 1).

A probabilistic sensitivity analysis was performed using a Monte Carlo simulation with 10,000 replications, and a cost-effectiveness acceptability curve (CEAC) constructed to

depict the probability of genotyping being cost-effective for a range of cost-effectiveness thresholds [42].

Scenario analysis

A scenario reflecting a single stage testing process was considered, at a cost of £20 per test. In order to simulate future price reduction of febuxostat, as may result following patent expiry, we explored the impact of equating the cost of febuxostat to that of allopurinol. We also present results from the first six months, corresponding with the time period where adverse events are most likely to occur.

We developed a scenario analysis which considered the case where patients experiencing SJS/TEN or DRESS with either allopurinol or febuxostat are treated symptomatically, which may reflect patients' reluctance to take further medicines following a serious adverse drug reaction [43].

We also assessed alternative scenarios for patients who test positive for *HLA-B*58:01*. Firstly, we considered such patients to be treated symptomatically, without maintenance uric acid lowering treatment, which may reflect a patient preference to discontinue treatment [44]. Secondly, we considered the scenario in which allopurinol would continue to be prescribed but that patients would be monitored closely. In this scenario, we assumed monitoring would also take place in patients prescribed febuxostat or symptomatic treatment, following experience of SJS/TEN or DRESS. Whilst the incidence of SJS/TEN or DRESS will not be affected by increased monitoring, early discontinuation of causative drug has been shown to improve mortality outcomes, with odds ratio 0.69 per day [45]. The cost of the monitoring service was based on 20 minutes of a pharmacist's time, costed at £71 per

hour, to allow for additional information at initiation, and two follow up phone calls during the first 6 months [46].

A scenario analysis which limits testing to patients with chronic renal insufficiency was assessed given this being an independent risk factor for SJS/TEN and DRESS in patients prescribed allopurinol, (relative risk compared with no chronic renal insufficiency 3.79; 95% CI 2.43, 5.92) [30]. Patients with chronic renal insufficiency (eGFR 15-29 mL/min/1.73m²) have a standardised mortality ratio of 3.2 (95% CI 3.1, 3.4) [25], and SJS/TEN is associated with increased mortality in this patient group (67% of patients experiencing SJS/TEN do not survive the ADR) [30]. The increased prevalence of SJS/TEN and associated mortality were modelled alongside reduced dose of allopurinol (100mg per day) and reduced dose colchicine (0.5mg per day) as recommended for this population [26].

As being female is associated with a higher risk of allopurinol induced SJS/TEN or DRESS (OR 1.45; 95% CI, 1.35-1.56) [9, 47], and that SJS/TEN and DRESS mortality is higher in females (OR 1.63; 95% CI, 1.28-2.08) [47] we conducted an analysis for a female population subgroup, aged 62.

Whilst the primary analysis is for a European population, the population of the UK is ethnically diverse. We conducted an analysis which considered an increased prevalence of *HLA-B*58:01*, based on a pooled analysis of populations of Asian ethnic origin, at 4.24% [9].

A further analysis was considered for the population with greatest prevalence of *HLA-B*58:01*, at 17% (the China Guangdong Province Meizhou Han population) [9].

Finally, as the long term impact of alternative treatments and the long term consequences of SJS/TEN or DRESS will have a greater lifetime impact on younger populations, we tested the cost-effectiveness of testing in a population of 35 year old males.

Results

The modelled rate of ADRs in the test group was 0.95 (95% central range [CR] (0.16, 3.04)) per 10,000 patients, compared with 1.83 (95% CR 0.40, 6.00) in the standard care group.

The number needed to screen in order to prevent one ADR (either SJS/TEN or DRESS) is 11,286 (95% CR 2,573, 53,594).

There is a small, but significant, incremental cost of £103 (95% CR £98, £106) associated with testing (Table 2). Cost differences are mainly attributable to drug costs and the cost of genotyping. There is also a very small QALY gain from testing, of 0.0023 (95% CR -0.0006, 0.0055), however this is not significant. QALY gains predominantly derive from better management of gout as febuxostat is more efficacious than allopurinol. The resulting ICER for *HLA-B*58:01* genotyping was £44,954 per QALY gained.

insert table 2 here

Parameter and structural sensitivity analysis

A tornado plot illustrating the sensitivity of the ICER to the 10 most influential parameters is shown in Figure 2. Univariately, the efficacy of febuxostat (risk ratio for achieving sUA < 360µmol/l versus allopurinol) and the cost of genotyping were most influential. The ICER was stable to variation in all other parameters within their 95% confidence interval.

Figure 3 presents the CEAC for the base case analysis, which indicates that the probabilities of genotyping being cost effective at ceiling ratios of £20,000 and £30,000 per QALY are 0.05 and 0.25, respectively.

insert figures 2 and 3 here

Scenario analyses (Table 3), indicate testing to be cost-effective within populations with a higher prevalence of *HLA-B*58:01* (at £27,218 and £22,359 per QALY gained, for 4.24% and 17% prevalence, respectively) where the number needed to screen to prevent one ADR reduces to 3,018 and 753; and when the cost of febuxostat is reduced to that of allopurinol, resulting in an ICER of £23,679 per QALY gained. A less expensive, single-stage test, reduces the ICER to £29,469 per QALY gained. In the case of both reduced price febuxostat and cheaper testing, the ICER is £8,195 per QALY gained.

insert table 3 here

Blanket prescription of allopurinol with only symptomatic treatment following ADR resulted in a reduction in both costs and QALYs. For other scenarios, and alternative modelling assumptions, ICERs remained higher than £30,000 per QALY. While the number needed to screen to prevent one case of SJS/TEN in patients with chronic renal insufficiency reduced to 2,964, testing remained not cost-effective at £38,478 per QALY gained. Based on a 12-month time horizon of analysis, the QALY gain, being almost solely attributable to the reduction in cases of SJS/TEN and DRESS, is very small, which inflates the ICER.

Discussion

Our model suggests that from a UK NHS perspective, routine genotyping for *HLA-B*58:01* is not cost-effective for preventing SJS/TEN and DRESS associated with allopurinol in patients with gout. The small QALY gain, equivalent to less than one quality-adjusted day, is commonplace in pharmacogenetic testing due to the low allele prevalence and rarity of the adverse event leading to a low PPV [48]. In scenario analyses, genotyping was modelled to be cost-effective when the price of testing reduced to \leq £21 per patient, or when the cost of febuxostat is reduced, such as might be expected once available generically, expected in 2019. The model was robust to the alternative assumption of no uric acid lowering treatment being prescribed following a serious ADR, which may reflect patient or prescriber preference [43].

We are aware of three existing economic evaluations of *HLA-B*58:01* screening for preventing allopurinol induced SCAR, with mixed results of cost-effectiveness [15, 16, 17]. Differences among these studies can be attributed to differences in populations but also methodological limitations which are addressed in our analysis.

Firstly, our analysis has strength in the use of febuxostat as a realistic and licensed comparator to allopurinol for a UK setting. Of the previously conducted economic evaluations, only Park [16] considered febuxostat as a comparator; both other studies consider probenecid as the comparator [15, 17], which has very limited use in the UK.

Secondly, previous economic evaluations made no consideration of the relative effectiveness of urate lowering drugs, and focused exclusively on differences in the rates of SCAR. The Thai analysis, for instance, assumed a single health utility applied to all patients regardless of treatment received [15]. This represents a major limitation, as febuxostat may

be more effective than allopurinol in lowering serum urate, if not in reducing the incidence of gout flares or tophus area [40]. By adopting a lifetime horizon of analysis that captured the differences in efficacy and costs between treatments, our analysis reduces this bias while also taking fully into account the long term sequelae of SJS/TEN and DRESS.

Only one previous economic evaluation has considered hypersensitivity reactions other than SJS/TEN [17], and we are the first to consider SJS/TEN and DRESS separately.

Our analysis also benefited from having modelled a number of potential patient populations, to reflect different clinical circumstances where genotyping may be cost-effective, as well as different scenarios of drug sequences in patients who experience ADRs and future decreases in the cost of testing and febuxostat.

As with any economic model, however, we were reliant on disparate sources of evidence and some assumptions were necessary. Firstly, we relied on unpublished data on utilities in gout. Alternative, published data of EQ-5D utilities in 110 patients, did not present utility by drug, disease severity or response to treatment, and were therefore unsuitable for populating the model [49]. However the mean utility value of 0.74 (SD 0.23) is consistent with the data used in our analysis.

Secondly, our analysis did not capture any adverse events other than SJS/TEN or DRESS, which may have implications, especially in chronic renal populations. Neither were other common comorbidities, such as cardiovascular disease and diabetes taken into account explicitly. However, with the assumption that the populations from which costs and utilities were sourced, were representative of a general gout population, such comorbidities would have been captured implicitly.

Thirdly, the scenario representing patients with chronic renal insufficiency did not account for costs or QALYs associated with the condition, but only the impact of the condition on SJS/TEN and DRESS, mortality and prescription costs. Moreover, there was no evidence as to whether the rate of SJS/TEN or DRESS in febuxostat treated patients with chronic renal insufficiency would be any higher than in the general population.

Fourthly, in the absence of data, we assumed that the probability of an increase in flares during the prophylaxis period is independent of the probability of achieving sUA < 360µmol/l.

Finally, we assumed that sUA remains constant after 12 weeks provided that treatment does not change. This is consistent with other economic evaluations [17, 18], and with results from the EXCEL study [20], but requires patients to be fully adherent, which may not be the case in practice [44]. The EXCEL study noted that after 24 months, 76% of patients prescribed febuxostat remained on treatment, whilst only 40% of patients persisted with allopurinol [20].

In conclusion, our analysis suggests that routine, prospective genotyping for *HLA-B*58:01* prior to the prescription of allopurinol for gout is not cost-effective in a UK NHS setting. There are, however, subpopulations where testing is more likely to be cost effective, including patients with chronic renal insufficiency, and populations with a higher *HLA-B*58:01* prevalence. Testing is expected to become cost-effective with reductions in the cost of genotyping, and with the future availability of cheaper, generic febuxostat.

Key messages

- *HLA-B*58:01* is associated with severe adverse drug reactions to allopurinol in patients with gout.
- Routine testing of gout patients for *HLA-B*58:01* is currently not cost-effective in the UK.
- *HLA-B*58:01* genotyping of gout patients is cost-effective if the price of testing and febuxostat reduces.

Conflict of interest statement

The authors declare no conflicts of interest.

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Table 1: Model inputs: Transition probabilities, costs and utilities

Parameter	Mean	Distribution for probabilistic sensitivity analysis	Univariate sensitivity analysis		Reference
			Lower range	Upper range	
Transition probabilities					
Prevalence of <i>HLA-B*58:01</i> (European mean)	0.0113	Beta(27340, 202446)	0.0108	0.0119	[9]
P(SJS/TEN allopurinol) within 3 months of initiation	0.0002	Normal(0.0002, 0.00007)	0.00002	0.0003	[15, 19]
P(DRESS allopurinol) within 3 months	0.0011	Beta(2, 1835)	0.0001	0.0030	[26]
P(SJS/TEN febuxostat) within 3 months of initiation	0.00010	Beta(1, 9999)	0.00000	0.00037	[23]
P(DRESS febuxostat) within 3 months of initiation	0.00010	Beta(1, 9999)	0.00000	0.00037	[23]

Sensitivity of test (SJS/TEN)	0.9285	Beta(144.64, 8.07)	0.8984	0.9732	Meta analysis
Specificity of test (SJS/TEN)	0.8907	Beta(311.64, 42.01)	0.8432	0.9110	Meta analysis
Sensitivity of test (DRESS)	0.9348	Beta(56.34, 3.93)	0.8387	0.9753	Meta analysis
Specificity of test (DRESS)	0.8470	Beta(20.51, 3.63)	0.6544	0.9441	Meta analysis
P(360µmol/l allopurinol)	0.3800	Beta(497.8, 812.2)	0.3539	0.4064	[27]
Proportion of non-responders with (360µmol/l < sUA < 475µmol/l allopurinol)	0.7900	Beta(641.638, 170.562)	0.7613	0.8173	[18]
Proportion of non-responders with (475µmol/l < sUA < 595µmol/l allopurinol)	0.1750	Beta(142.135, 670.065)	0.1497	0.2019	[18]
Proportion of non-responders with (sUA > 595µmol/l allopurinol)	0.0350	Beta(28.247, 783.773)	0.0235	0.0487	[18]
Risk ratio UA febuxostat vs allopurinol	1.8182	Gamma(208.2823, 0.0088)	1.5873	2.0833	[28]
P(360µmol/l febuxostat)	0.6909				RR*allopurinol

Proportion of non-responders with (360µmol/l < sUA < 475µmol/l febuxostat)	0.7410	Beta(299.5796, 104.7113)	0.6973	0.7825	[18]
Proportion of non-responders with (475µmol/l < sUA < 595µmol/l febuxostat)	0.2130	Beta(86.114, 318.177)	0.1745	0.2542	[18]
Proportion of non-responders with (sUA > 595µmol/l febuxostat)	0.0460	Beta(18.597, 385.694)	0.0278	0.0684	[18]
Risk risk sUA none vs allopurinol	0.0203	Gamma(0.0898, 0.1586)	0.0029	0.1439	[27]
Proportion of non-responders with (360µmol/l < sUA < 475µmol/l no treatment)	0.7900	Beta(641.638, 170.562)	0.7613	0.8173	As for allopurinol
Proportion of non-responders with (475µmol/l < sUA < 595µmol/l no treatment)	0.1750	Beta(142.135, 670.065)	0.1497	0.2019	As for allopurinol

Proportion of non-responders with (sUA > 595µmol/l no treatment)	0.0350	Beta(28.247, 783.773)	0.0235	0.0487	As for allopurinol
P(initial flares allopurinol)	0.1402	Beta(166, 1184)	0.1210	0.1605	[29, 30, 31]
Risk ratio of initial flare, febuxostat vs allopurinol	1.3130	Gamma(43.2461, 0.0311)	0.9730	1.7720	[28]
P(acute flares sUA < 360µmol/l)	0.0874	Beta(311.5008, 3252.5819)	0.0784	0.0969	[18]
P(acute flares 360µmol/l < sUA < 475µmol/l)	0.0989	Beta(307.8354, 2804.7567)	0.0887	0.1096	[18]
P(acute flares 475µmol/l < sUA < 595µmol/l)	0.1085	Beta(304.4738, 2501.7361)	0.0973	0.1203	[18]
P(acute flares sUA > 595µmol/l)	0.1161	Beta(301.9822, 2299.0704)	0.1041	0.1287	[18]
Mortality *		Assumed fixed as based on entire population			[32]
Mortality: SJS/TEN	0.2652	Beta(122, 338)	0.2259	0.3065	[6]
Mortality: DRESS	0.1000	Beta(13.73, 123.57)	0.0558	0.1552	[7]

Utilities

*Gout with sUA < 360µmol/l	0.7463	1-Beta(98.9914, 291.1993)	0.7020	0.7882	[18]
*Gout with 360µmol/l < sUA < 475µmol/l	0.7120	1- Beta(121.7288,300.9406)	0.6680	0.7541	[18]
*Gout with 475µmol/l < sUA < 595µmol/l	0.6777	1- Beta(145.1274,305.1592)	0.6339	0.7200	[18]
*Gout with sUA > 595µmol/l	0.6435	1- Beta(168.6184,304.3645)	0.5998	0.6860	[18]
Disutility: Gout flare	0.0097	Beta(15.8351, 1616.6494)	0.0055	0.0150	[18]
Disutility: SJS/TEN – acute	0.1400	Gamma(3.7867, 0.1901)	0.1869	1.6054	[33]
Disutility: SJS/TEN – long term	0.1149	Gamma(0.4423, 0.2597)	0.0000	0.6102	[34]
Disutility: DRESS - acute	0.1430	Gamma(0.9086, 0.1574)	0.0026	0.0121	[35]
Disutility: DRESS – long term	0.1149	Gamma(0.4423, 0.2597)	0.0000	0.6102	[34]
Resource use and costs					
Cost: Gout flare	321.62	Gamma(16, 20.1011)	183.83	497.31	[18]
Cost: Gout maintenance	97.40	Gamma(16, 6.0874)	55.67	150.60	[18]

Cost: Allopurinol 300mg	3.77	Fixed	3.41	4.15	[26]
Cost: Febuxostat 80mg	79.17	Fixed	71.60	87.11	[26]
Cost: Colchicine 1mg (500 microgram BID)	65.92	Fixed	59.62	72.54	[26]
Cost: SJS/TEN – acute	31,232.00	Gamma(1.18, 25262.51)	1,626.72	103,207.86	[36]
Cost: SJS/TEN – long term	140.00	Gamma(3.84, 42.17)	0.00	280.00	Expert opinion
Cost: DRESS - acute	£11,209.03	Gamma(7.44, 1507.13))	£4658.78	£20,585.50	[36]
Cost of <i>HLA-B*58</i> screen	54.29	Fixed	10.00	90.00	[36]
Cost of <i>HLA-B*58:01</i>	94.91	Fixed	30.00	150.00	[36]

Abbreviations: SJS Steven-Johnson syndrome, TEN toxic epidermal necrolysis, DRESS drug reaction with eosinophilia and symptomatic symptoms, P probability, sUA serum uric acid concentration, RR risk ratio, BID twice a day

*Tested simultaneously as 'Utility of gout' in univariate sensitivity analysis to preserve natural ordering

Table 2: Results of the base-case analysis

	Test		Standard care		Incremental	
	Cost	QALYs	Costs	QALYs	Costs	QALYs
Gout management	£5,597	10.3400	£5,596	10.3378	£0.06	0.0022
Gout flare management (prophylaxis)	£45.26	-0.0003	£45.10	-0.0003	£0.16	0.0000
Gout flare management (non-prophylaxis)	£1,741	-0.0131	£1,742	-0.0131	-£0.82	0.0000
Treatment of SJS/TEN and DRESS	£1.27	-0.000004	£2.53	-0.000012	-£1.26	0.0000
Managing sequelae of SJS/TEN and DRESS	£0.06	-0.0001	£0.14	-0.0003	£-0.08	0.0001
Genotyping	£55.50		£0		£55.50	
Drug cost	£333.79		£284.30		£49.49	
Total	£7,773	10.3264	£7,671	10.3241	£103.05	0.0023

Abbreviations: SJS Steven-Johnson syndrome, TEN toxic epidermal necrolysis, DRESS drug reaction with eosinophilia and symptomatic symptoms, QALY quality-adjusted life-year

Table 3: Results of scenario analyses

	Incremental Cost (per patient)	Incremental QALY (per patient)	Number needed to screen to prevent one ADR	ICER (Cost/QALY)
Base case	£103.05	0.0023	11,286	£44,954
Results at 6 months	£56.81	0.0001	11,286	£706,624
35 year old male	£128.68	0.0035	11,286	£36,571
62 year old female	£107.06	0.0026	10,437	£41,176
Chronic renal insufficiency*	£84.46	0.0022	2,964	£38,478
Prevalence of <i>HLA-B*58:01</i> 4.24%	£233.34	0.0086	3,018	£27,218
Prevalence of <i>HLA-B*58:01</i> 17%	£768.55	0.0344	753	£22,359
Set comparator ULA cost equal to allopurinol**	£54.28	0.0023	11,286	£23,679
Single stage test, cost £20	£67.55	0.0023	11,286	£29,469
All prescribed allopurinol. No ULA in case of ADR	-£0.72	-0.0001	***	£11,081^

Test negative: Allopurinol; Test positive: Febuxostat; No ULA in case of ADR	£102.69	0.0023	11,284	£45,456
Test negative: Allopurinol; Test positive: No ULA; No ULA in case of ADR	£51.18	-0.0024	11,003	Dominated
Test negative: Allopurinol; Test positive: Allopurinol with increased monitoring; Febuxostat in case of ADR	£55.82	0.0000	***	£1,783,994

Abbreviations: QALY quality-adjusted life-year, ICER incremental cost effectiveness ratio, ADR adverse drug reaction, ULA urate lowering agent, PPV positive predictive value, NPV negative predictive value

*Chronic renal insufficiency: SJS/TEN PPV 0.0048; SJS/TEN NPV 1.0000; DRESS PPV 0.0251; DRESS NPV 0.9997.

**Colchicine maintained for 6 months due to prophylaxis flare rate

***In excess of the number of people with gout in the UK

^Less costly and less effective

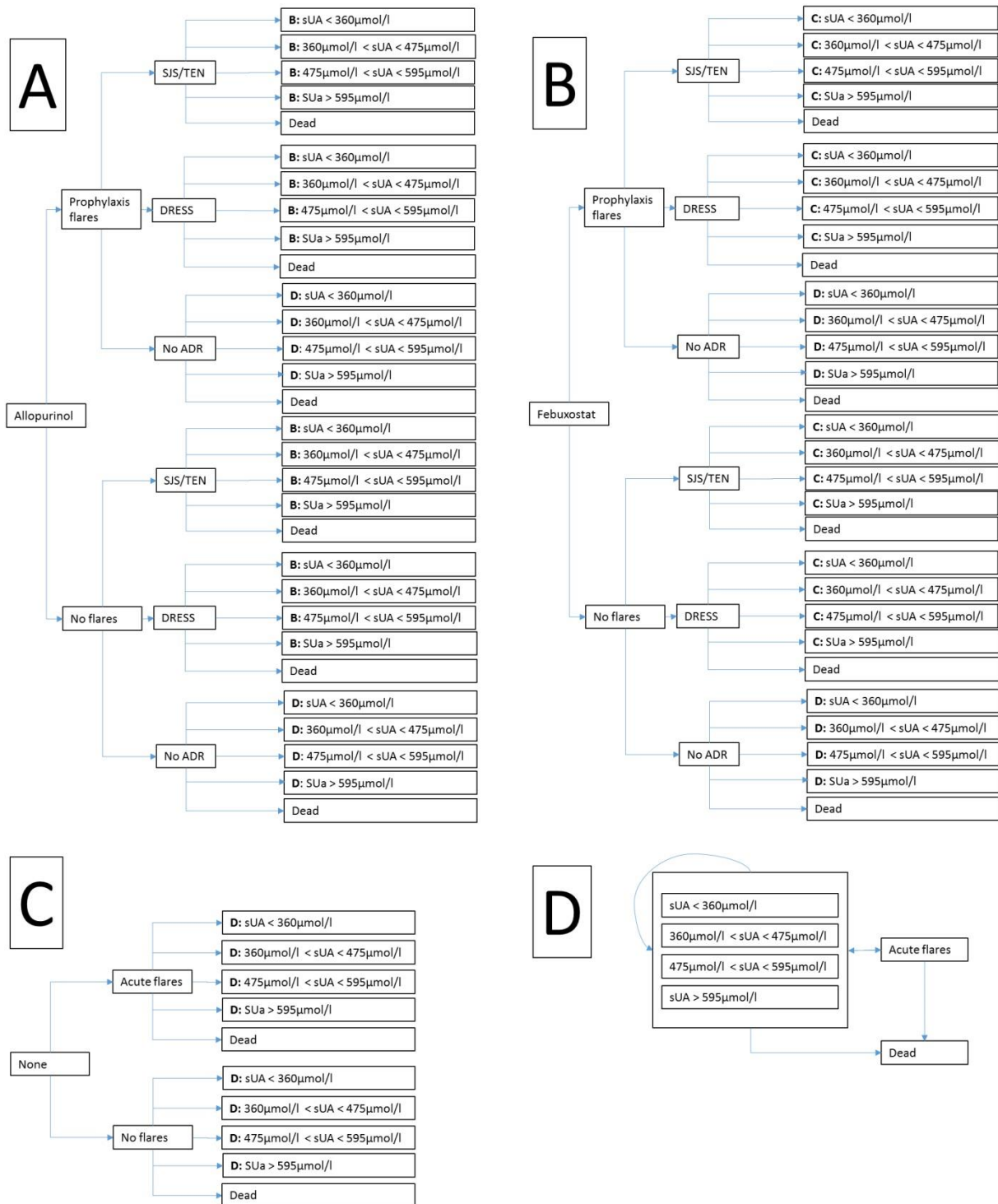


Figure 1: Schematic representation of the decision analytic model. Patients in the ‘no test’ scenario all enter the model at A, whilst patients in the ‘test’ scenario enter the model in either A or B dependent upon test result. Patient flow between each 3-month model is represented at the leaf nodes. Where patients reach the Markov model (model D) before the end of 12-months, the first cycles (up until 12-months) are treated as the run in period.

Abbreviations: SJS Steven-Johnson syndrome, TEN toxic epidermal necrolysis, DRESS drug reaction with eosinophilia and symptomatic symptoms, sUA serum uric acid concentration

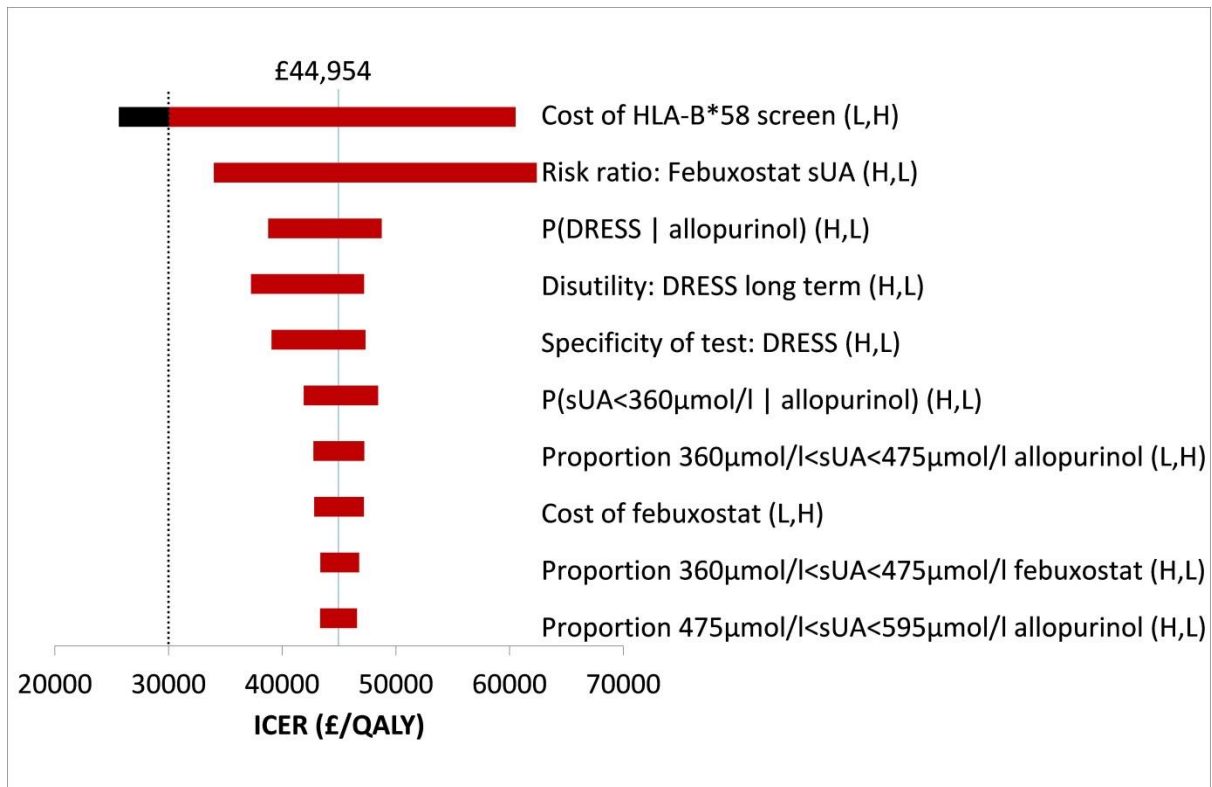


Figure 2: Tornado plot illustrating univariate sensitivity analysis. (L,H) and (H,L) indicate whether the range tested is displayed as low-high or high-low, respectively. The vertical line at £44,954 per QALY gained represents the ICER corresponding to the base case analysis.

Abbreviations: sUA serum uric acid concentration, ICER incremental cost effectiveness ratio, QALY quality-adjusted life-year

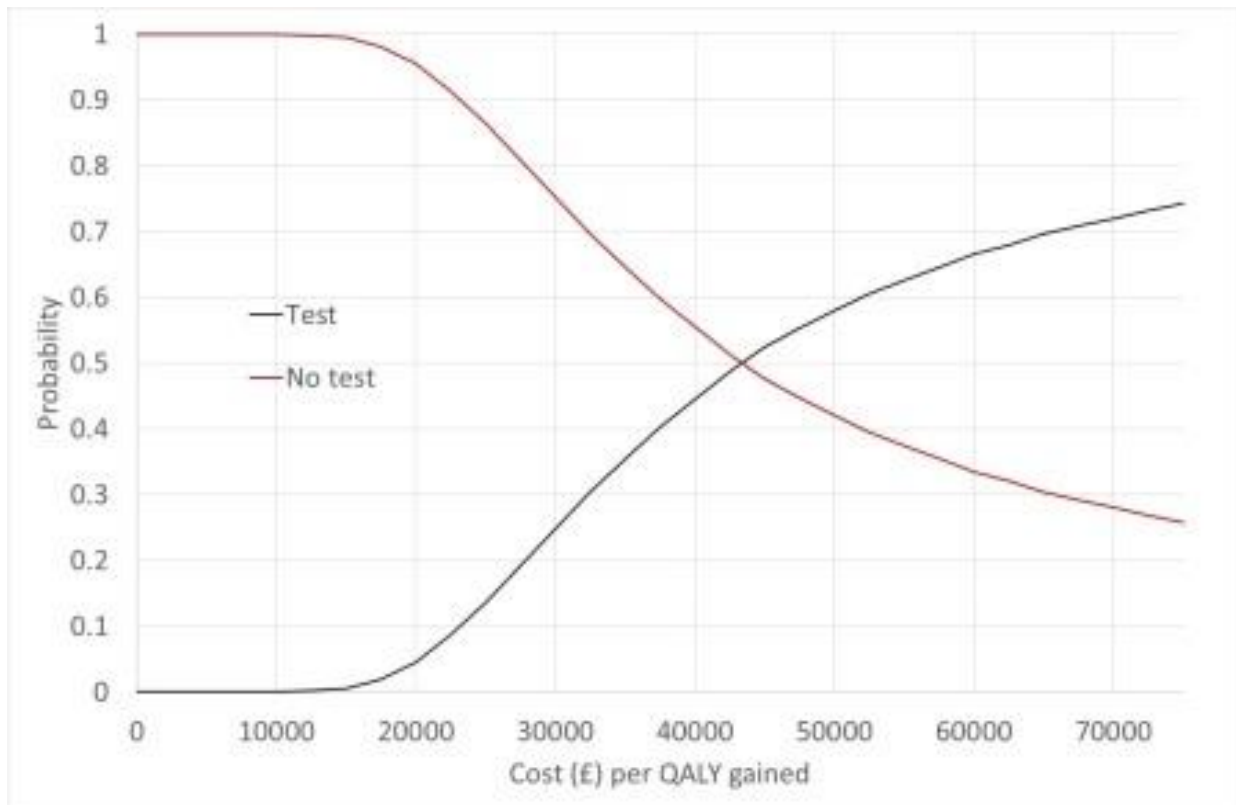


Figure 3: Cost effectiveness acceptability curve indicating the probability of testing being cost-effective for a range of threshold values.

Abbreviations: QALY quality-adjusted life-year